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09/747,521	12/21/2000	Darrel R. Galloway	22727/04079	9991

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EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	13

DATE MAILED: 07/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/747,521	Applicant(s) GALLOWAY ET AL.	
	Examiner Khatol S Shahnan-Shah	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) *25,28-30 and 32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26,27,31 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *23-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' information disclosure statements, received April 30, 2001 and July 18, 2001 papers # 3 and 8 are acknowledged.

2. Applicants' preliminary amendments, received 1/24/2002, paper # 10 is acknowledged. Claims 1-22 were canceled without prejudice. Claims 23-25 were amended. New claims 31-42 were added.

3. Applicants' supplemental preliminary amendments, received 4/01/2002, paper # 12 is acknowledged. Claims 23 and 31 were amended. New claims 43-44 were added.

Election/Restrictions

4. Applicants' election with out traverse of 4/01/2002 in Paper No. 12 is acknowledged. Applicants elected Group III (claims 23-24, 26-27, 31, 41-44), which are drawn to nucleic acid. In response to the request of election of Species, applicants elected the species of claim 31.

5. Claims 25, 28-30, and 32-40 are withdrawn from further consideration pursuant to37 CFR 1.142(b), as being drawn to non-elected inventions.

6. Currently claims 23-44 are pending.

7. Claims 23-24, 26-27, 31, 41-44 are and under consideration.

Drawings

8. The drawings are objected to by the Draftsperson under 37 CFR 1.84 or 1.152. See attached form PTO 948.

Abstract

9. This application contains two abstracts of disclosure one submitted as page 26 of the original disclosure and another submitted 4/26/2001 paper # 6. Applicants are advised to cancel one of these abstracts.

Specification

10. The disclosure is objected to because of the following informalities:

This specification contains sequences in the specification which does not comply to 37 CFR 1.821 (d) for failing to reference to the sequences by use of sequence identifiers, preceded by " SEQ ID NO" in the text of description. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 23-24, 26-27, 31 and 41, 42 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid base immunogenic composition, does not reasonably provide enablement for a vaccine and immunogenic fragments of said composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to an immunogenic composition complex vaccine against *Bacillus anthracis* comprising a first polynucleotide which encodes mutated lethal factor (LF) protein or immunogenic fragments of said protein and a second polynucleotide which encodes *Bacillus*

anthracis protective antigen (PA) and immunogenic fragments of said antigen. The claims are extremely broad covering any immunogenic fragment of the claimed nucleic acid.

The specification fails to set forth sufficient evidence showing that the claimed vaccine complex could be made with "dual molecules" of claim 42 wherein the first and second polynucleotides are incorporated in the same viral vector.

Further, the specification does not allow one of skill in the art to fully understand the association between the multiple components present in the "complex". For example, the optimal amounts or proportions of different "bacterial protein fractions", i.e., protective antigen protein and/or lethal factor protein, that should be present in the complex such that the complex can accomplish its alleged immunogenic and/or preventive functions are not disclosed. It is also not clear from the specification what is encompassed by the first polynucleotide and the second polynucleotide. What sequences encompass each of these polynucleotides?

The prior art teaches that *Bacillus anthracis* vaccines are unpredictable, specifically, in the type of effect they will have on preventing or treating infection and the ability to reasonably predict the role of lethal toxin *in vivo*. Two types of anthrax vaccines are licensed for use in humans: the spores of the toxigenic, nonencapsulated *Bacillus anthracis* STI-1 strain and the cell free PA- based vaccines consisting of aluminium hydroxide –adsorbed supernatant material from cultures of toxigenic nonencapsulated *Bacillus anthracis* strain V770-NPI-R. The use of live attenuated STI-1 occasionally results in general and local adverse responses. Furthermore it was reported that STI-1 vaccine has a relative low immunogenicity (Cohen et al., Infection and Immunity, 2000). To increase immunity a combined vaccine of live STI-1 supplemented with cell-free PA formulation was evaluated and proposed for veterinary use. While cell-free PA

based vaccines appear to be safer; they require numerous boosters (Cohen et al., page 4549). It appears, therefore, that there is a need for a safe and more efficient vaccine, which could generate stable and prolonged immunity in humans.

In the instant specification no art recognized *in vitro* or *in vivo* models are shown in which protection is produced from instantly claimed invention and correlated to protection in humans.

Claims are also directed to a genus of isolated nucleic acid molecules, which encode fragments of a polypeptide comprising the amino acid sequence of SEQ ID NO 2. The specification does not provide any description of which positions can be altered without loss of protein activity or which position would render a protein non-functional. Furthermore, no examples of any of these fragments are provided. The specification has no disclosure of the function of these fragments of the polypeptides encoded by the nucleic acid molecules of which have at least 90% sequence identity to SEQ ID No: 2. Each genus of the polynucleotides claimed is a large variable genus including nucleic acid molecules encoding polypeptides, which can have a wide variety of functions. Therefore, many functionally unrelated variants (polynucleotides and polypeptides) are encompassed within the scope of the claims.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e.

expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. Multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does **not** disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity if the intact protein; and

- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant has **not** provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed.Cir.1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S.P.Q. 546(Bd. Pat. App. & Int. 1986).

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the court of appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988).

These factors include 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, and 8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the

specification with respect to a vaccine complex having claimed functional feature of capability of generating protective responses, 3) there are no working examples which suggest the desired results of a vaccine against *Bacillus anthracis*, 4) the nature of the invention involved the complex and incompletely understood area of protective immune responses against *Bacillus anthracis*, 5) the state of the prior art shows the lack of correlates to immunity with *Bacillus anthracis* , 6) the relative skill of those in the art is commonly recognized as quite high (post – doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, and lack of guidance on how to obtain the desired effect using the claimed vaccine complex it is determined that it would require undue experimentation to make and/or use the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 23-24, 26-27, 31 and 41-44 are rejected under 35 U.S.C. 102 (b) as being anticipated by Leppela et al. (US Patent No. 5,591,631).

The claims are drawn to a nucleic acid composition comprising a first polynucleotide which encodes a mutated lethal factor protein (LF) and second polynucleotide, which encodes a *Bacillus anthracis* protective protein antigen (PA).

Note: The examiner views the claims as a product (i.e composition) the use of the composition does not impart any criticality in the patent ability of the product.

Leppela et al. disclose a nucleic acid composition comprising a first polynucleotide which encodes a mutated lethal factor protein (LF) (see column 1, lines 35-45) and second polynucleotide, which encodes a *Bacillus anthracis* protective protein antigen (PA). (see abstract and claim 1). The examiner views Leppela's LF protein lacking the catalytic domain the same as the mutated LF taught by the applicants. Leppela et al. teach promoters and DNA sequences which are being operably linked to promoters (see column 6, lines 40-65). Leppela et al. teach vectors including viral vectors (columns 6 lines 40 –44 and column 8, lines 4-10). Leppela et al. teach sequences which are > 90% identical to the sequence extending from amino acid 9- 252 of SEQ ID # 2 (see Leppela et al. SEQ ID # 6 columns 53-56 and attached sequence alignment). The prior art teaches the claimed invention.

Since the office does not have the facilities for examining and comparing applicants' product with the product of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i. e., that the product of prior art does not possess the same material structure and functional characteristics of the claimed product). See In re Best, 562 F.2 d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusions

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30am-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

June 26,2002

MARK NAVARRO
PRIMARY EXAMINER